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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 10/654,796 | 09/03/2003 | Nicholas P. Barker | 50206/013003 | 5419 |

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| EXAMINER | |
|---|---|
| HISSONG, BRUCE D | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1646 | |

DATE MAILED: 11/27/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/654,796 | BARKER ET AL. | |
| | Examiner | Art Unit | |
| | Bruce D. Hissong, Ph.D. | 1646 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *15 September 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-3,5-7 and 9-29* is/are pending in the application.

4a) Of the above claim(s) *22-29* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,5-7 and 9-21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

***Formal Matters***

1. The Applicants' response to the office action mailed on 3/15/2006, including arguments/remarks and amendments to the claims and specification, was received on 9/15/2006 and has been entered into the record.

2. The Applicants' amendments to the claims have cancelled claims 4 and 8. Therefore, claims 1-3, 5-7, and 9-29 are currently pending. Claims 22-29 are withdrawn as non-elected subject matter. Claims 1-3, 5-7, and 9-21 are the subject of this office action.

3. The text of those sections of Title 35, U.S.C. not included in this action can be found cited in full, in the previous office action mailed on 3/15/2006.

***Specification***

The objection to the specification regarding improper designation of trademarks, as set forth on page 4 of the office action mailed on 3/15/2006, is *withdrawn* in response to Applicants' amendments to the specification to properly identify trademarks.

***Claim Rejections - 35 USC § 112, second paragraph***

Rejection of claims 1-3, 5-7, and 9-21 under 35 USC § 112, second paragraph, for being indefinite regarding the metes and bounds of asialo-interferons, as set forth on pages 4-5 of the prior office action mailed on 3/15/2006, is withdrawn in response to Applicant's arguments that the instant specification adequately defines the term "asialo-interferon" on page 5, line 24 – page 6, line 14.

***Claim Rejections - 35 USC § 102***

Claims 1-3, 7, 11-12, and 15-21 *remain rejected* under 35 USC § 102(e) as being anticipated by DeFrees *et al* (US 2004/0082026), as set forth on page 5 of the office action mailed on 3/15/2006. The claims of the instant invention are drawn to a modified asialo-interferon, wherein said asialo-interferon is modified by conjugation to a water-soluble polymer having a molecular weight of approximately 1,000 to 60,000 daltons, and more specifically 10,000 – 20,000 daltons, and wherein said modification is via pegylation or pvpylation. The claims also recite asialo-interferon that is interferon-α, -β, or –γ, and is also recites human asialo-interferon. Finally, the claims also are drawn to pharmaceutical compositions of modified asialo-interferons.

As set forth on page 5 of the office action mailed on 3/15/2006, DeFrees specifically teaches pegylation of asialo-interferons, including interferon-α and –β (paragraphs 1683-1701), and specifically teach pegylation with polyethylene glycol of 10,000 – 20,000 daltons (paragraph 1689). DeFrees also teaches pvpylation of IFN polypeptides (paragraph 0734), and teaches pharmaceutical compositions of modified asialo-interferon polypeptides (paragraph 0117).

In the response received on 9/15/2006, the Applicants amended independent claim 1 to recite a modified asialo-interferon that is conjugated to a water-soluble polymer, wherein said conjugation to a water-soluble polymer is at a cysteine, lysine, serine, threonine, tyrosine, aspartic acid, or glutamic acid residue, or at a C-terminal carboxyl, or at an N-terminal amine. The Applicants argue that DeFrees does not meet the limitations of any claim of the instant invention because DeFrees does not specifically teach a water-soluble polymer conjugated to an asialo-interferon at any of the specifically claimed amino acid residues.

This argument has been fully considered and is not persuasive. Although DeFrees does not explicitly recite any specific asialo-interferon amino acid to which a water-soluble polymer may be attached, DeFrees does teach pegylation of lysine residues in other polypeptides (paragraph 0681), and also teaches covalent modifications of peptides, such as pegylation, at various amino acid residues, including cysteine, lysine tyrosine, serine, and threonine, as well as terminal amino-acid residues (paragraph 1010). Thus, although DeFrees does not specifically teach asialo-interferons conjugated to water-soluble polymers at any specific amino acid residue, it would be expected, in the absence of evidence to the contrary, that an asialo-interferon polypeptide that is pegylated or pvpylated by the methods disclosed in DeFrees would contain at least one cysteine, lysine, serine, threonine, tyrosine, aspartic acid, or glutamic acid

residue, or a c-terminal carboxyl, or an N-terminal amine, that is conjugated to a water-soluble polymer. Because the Office does not have the facilities for testing the asialo-interferons taught by DeFrees, the burden is on the applicant to show a novel and unobvious difference between the claimed modified asialo-interferon and that of the prior art. See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray, 10 USPQ 2d 1922 1923 (PTO Bd. Pat. App. & Int.). Thus, for the reasons set forth above, DeFrees meets the limitations of claims 1-3, 7, 11-12, and 15-21 of the instant application.

***Claim Rejections - 35 USC § 103***

*Rejections maintained*

1. Claims 5-6 *remain rejected* under 35 USC § 103(a) as being obvious over the combination of DeFrees *et al*, Monkarsh *et al*, and Shadle *et al*, as set forth on page 6 of the office action mailed on 3/15/2006. Claims 5-6 of the instant invention are drawn to a pegylated asialo-interferon, wherein said pegylated asialo-interferon is pegylated on a cysteine (claim 5) or lysine (claim 6) residue.

In the response received on 9/15/2006, the Applicants argue that DeFrees teaches away from the claimed asialo-interferons because it teaches, in paragraph 0003, that peptides lacking a terminal sialic acid residue are rapidly removed by the liver, which negates any potential therapeutic of the peptide. The Applicants further argue that neither Monkarsh or Shadle teach, suggest, or motivate a skilled artisan to create asialo-interferons, and therefore claims of the instant invention are not obvious in view of the combination of DeFrees, Monkarsh, and Shadle.

These arguments have been fully considered and are not persuasive. First, it is noted that although DeFrees teaches that polypeptides lacking a terminal sialic acid residue are rapidly cleared from the circulation by the liver, pegylation of proteins may block this clearance of proteins (paragraph 0424), thus increasing the serum concentration of said proteins. Thus, a skilled artisan would know that the rapid clearance of asialo-interferons could be overcome by pegylation. Secondly, as stated in the rejection under 35 U.S.C. 102(e) above, DeFrees clearly teaches pegylation of asialo-interferons (paragraphs 1683-1701). In this light, DeFrees does not teach away from the use of asialo-interferons, but in fact teaches pegylation of asialo-interferons, and by teaching that pegylation improves the serum-half life of proteins, provides

the rationale, and thus motivation, for pegylation of asialo-interferons. Monkarsh and Shadle teach methods of pegylation on lysine and cysteine residues, respectively. Therefore, one of ordinary skill in the art, by following the teachings of DeFrees, would be motivated to pegylate asialo-interferons, and the teachings of Monkarsh and Shadle would provide the motivation, and methods, for specifically pegylating asialo-interferons on lysine or cysteine residues, respectively.

2. Claims 13-14 *remain rejected* under 35 USC § 103(a) as being obvious over the combination of DeFrees *et al* and Shadle *et al*, as set forth on pages 6-7 of the office action mailed on 3/15/2006. Claims 13-14 of the instant invention are drawn to asialo-interferons comprising additional cysteine residues compared to the mature polypeptide sequence. The teachings of DeFrees and Shadle are discussed *supra*.

In the response received on 9/15/2006, the Applicants argue that neither DeFrees or Shadle, alone or in combination, render the claimed invention obvious for the reasons set forth in the discussion of the preceding rejection under 35 U.S.C. 103(a). This argument has been fully considered and is not found persuasive for reasons set forth above, and for the reasons of record set forth in the previous office action mailed on 9/15/2006.

3. Claims 1-3, 5-7, and 9-21 *remain rejected* under 35 USC § 103(a) as being obvious over the combination of Smith *et al*, Monkarsh *et al*, Shadle *et al*, and Francis, as set forth on pages 7-8 of the office action mailed on 3/15/2006. The subject matter of the claims of the instant application, and the teachings of Monkarsh and Shadle, is discussed supra. Smith discloses production of human interferon-b in insect cells, and therefore teaches production of asialo-interferon-b due to the inability of insect cells to sialylate polypeptides. Francis *et al* teaches both pegylation and pvpylation of proteins, and teaches that such modification overcomes problems associated with rapid clearance of proteins or proteolytic degradation (see 1st paragraph, and Table 1).

In the response received on 9/15/2006, the Applicants argue that the Examiner has used hindsight reconstruction in the rejection, and that there is no showing of *prima facie* obviousness because the cited combination of references merely represent a piecing together of all the elements of the claimed invention, and do not suggest, teach, or motivate a person of skill in the art to combine said references.

These arguments have been fully considered and are not persuasive. In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

In the instant case, Smith teaches production of interferon-β, which by virtue of being produced in insect cells, would be asialo-interferon-β. Smith also teaches that interferon-β is known to have antiviral, antiproliferative, and anti-tumor properties, and would therefore be useful in medical applications (p. 2156, 2nd column, last paragraph). Even if Smith did not teach this, these properties of interferons are well-known in the art, and would provide motivation to use interferon-β to treat viral or neoplastic disease. Francis teaches that the half-life of proteins can be improved by modification by pegylation or pvpylation. Thus, by following the combined teachings of Smith and Francis, one of skill in the art would know of a polypeptide, interferon-b, that is useful for treating antiviral or neoplastic disease, and would also know of a way to improve the efficiency of interferon-β treatment by pegylation or pvpylation to increase its serum half-life. Finally, Monkarsh and Shadle disclose methods of pegylating specific residues. Therefore, the combined teachings of Smith, Francis, Monkarsh, and Shadle provide not only the motivation to pegylate or pvpylate an asialo-interferon-β polypeptide, but also provide a reasonable expectation of success by disclosing specific methods by which asialo-interferon-β can be pegylated.

Rejections necessitated by amendment

4. Claims 1-3, 7, and 9-12, and 15-21 are rejected under 35 U.S.C. 103(a) as being unpatentable over DeFrees *et al*, in view of Monkarsh *et al* or Shadle *et al*. The subject matter of the claims of the instant invention, and the teachings of DeFrees, Monkarsh, and Shadle are discussed *supra*.

Claim 1, as currently amended, is drawn to a modified asialo-interferon that is conjugated to a water-soluble polymer, wherein said conjugation to a water-soluble polymer is at a cysteine, lysine, serine, threonine, tyrosine, aspartic acid, or glutamic acid residue, or at a

C-terminal carboxyl, or at an N-terminal amine. As set forth above, DeFrees teaches pegylation or pvpylation of asialo-interferons. Although DeFrees does not specifically recite asialo-interferons pegylated or pvpylated on specific amino acid residues, the disclosure of DeFrees does teach pegylation of lysine residues in other polypeptides (paragraph 0681), and also teaches covalent modifications of peptides, such as pegylation, at various amino acid residues, including cysteine, lysine tyrosine, serine, and threonine, as well as terminal amino-acid residues (paragraph 1010). Thus, the disclosure of DeFrees would teach a skilled artisan modification of asialo-interferons by pegylation or pvpylation, and would also teach the skilled artisan that such modifications can be made by modification of specific amino acid residues, such as cysteine, lysine, threonine, tyrosine, and serine. Furthermore, as discussed supra, DeFrees also teaches the therapeutic benefits of pegylation or pvpylation of asialo-interferons.

Therefore, one of skill ordinary skill in the art would have been motivation, at the time the instant invention was conceived, to combine the teachings of DeFrees with those of either Shadle or Monkarsh to practice the instant invention as currently claimed. . By teaching pegylation/pvpylation of asialo-interferons and the therapeutic benefits of such modification, DeFrees provides the motivation to pegylate/pvpylate asialo-interferons, including human interferons $\alpha$, $\beta$, and $\gamma$; while Monkarsh and Shadle provide methods for pegylation of specific amino acid residues, and thus provide the motivation to pegylate asialo-interferon on lysine or cysteine residues, respectively.

***Conclusion***

No claim is allowable.

**THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,

however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bruce D. Hissong, Ph.D., whose telephone number is (571) 272-3324. The examiner can normally be reached M-F from 8:30 am - 5:00 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Nickol, Ph.D., can be reached at (571) 272-0835. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

BDH
Art Unit 1646

ROBERT S. LANDSMAN, PH.D
PRIMARY EXAMINER